Cross-Talk Between Constitutive and Inducible Nitric Oxide Synthases

To the Editor,

We read with great interest the recent work by Kanno et al describing the protective effect of nitric oxide (NO) against myocardial ischemia/reperfusion injury and were struck by the other phenomenon associated with it: superinduction of inducible NO synthase (iNOS) in endothelial NO synthase (eNOS) knockout mice. Although the exact mechanism is unknown and apparently “paradoxical,” the absence of constitutive NO seems to increase inducible NO production. In this respect, the authors argued that the effect could be due to redox stress associated with the absence of NO.

Recently, we published an article suggesting cross-talk between constitutive and inducible NO synthase (iNOS) using NO as a modulator. In particular, low (ie, physiological) NO levels inhibit iNOS transcription by inactivating nuclear factor-kB (NF-kB). However, when NO levels decrease beneath a putative threshold value (eg, as in eNOS knockout cardiomyocytes), they may not be sufficient to keep NF-kB suppressed, thus creating the favorable conditions for superinduction of NO synthase II (NOS-II) expression. Interestingly, the adaptive mechanism that the authors propose may simply reflect an acquired activation of NF-kB due to the absence of NO, leading to the change in redox stress.

Therefore, the work by Kanno et al introduces, for the first time, an ex vivo model indicating that intracellular amounts of NO may play a key role in modulating iNOS expression, thus providing further evidence for our hypothesis. However, other ex vivo or in vivo models should be examined to obtain more insight regarding the strict cross-talk between NO and NO synthases.

Moreover, on the basis of evidence suggesting a beneficial effect of iNOS-producing NO, very low amounts of NO, which could potentially be harmful to the body by facilitating the induction of iNOS expression, may not (for the same reason) always be detrimental. The work by Kanno et al pointed out the importance of the physiologically present NO in downregulating the induction of iNOS. Attention should be paid to any trial that modulates intracellular amounts of NO. Any compound downmodulating the catalytic activity of constitutive NO synthase, such as specific inhibitors of constitutive NO or NO donors that moderately increase intracellular NO levels, may exert more profound effects on the induction of iNOS expression than normally expected.

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